4th CONGRESS OF THE INTERNATIONAL
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JULY 10 - 14, 1961
GENEVA, SWITZERLAND

PHYSIOPATHOLOGY OF DIABETES

ROLE OF ENDOCRINE GLANDS IN EXPERIMENTAL DIABETES

BERNARDO A. HOUSSAY, M. D. (Buenos Aires)

REPORT READ ON THE 10th JULY, 1961

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LIVER - In the normal or diabetic condition the liver plays a fundamental homeostatic role, since it is the organ that produces glucose and thus governs the blood sugar level (28). The glucose output from the liver is increased by hypoglycemia and decreased by hyperglycemia. When the liver is absent, diabetic hyperglycemia cannot occur and it is not maintained if it already existed.

REGULATION OF SECRETION OF HORMONES - The secretion of each hormone is regulated and there is reciprocal balance among them.

PANCREAS - Insulin secretion maintains the normal blood sugar level, and prevents it from rising; it increases the uptake and utilization of glucose by the cells and its conversion to fat, glycogen or protein, or into carbon dioxide and water. Synthetic reactions are stimulated by insulin: fat synthesis, glycogen storage, protein anabolism and growth. The nature and extent of these reactions depending on the tissues and their conditioning.

Insulin must be present for other hormones can produce protein anabolism and growth (somatotropin, etc.). In absence of insulin protein catabolism is increased.

Insulin has a fat-synthesizing action. Without insulin fat synthesis is deficient or suppressed; and there is an increase of fat transport from depots to the liver, followed by intense hepatic ketogenesis.

There is still discussion as to whether the principal action of insulin is to increase transference of glucose into the cells, or is exerted on the chemical transformation of sugar.

The physiological role of glucagon is still in discussion. Large doses can produce a permanent (metaglucagon) diabetes (26).

Insulin is produced in the β cells of the islets of Langerhans. In islets isolated by microdissection the insulin content is about 100 times larger than in total pancreas (which has about 1 p 100 of islets). The amount of insulin secreted, as measured by the substitution method, is around 0.01 units/kg/h (0.005-0.02 units)

in the dog (21). The detection and estimation of blood insulin is made principally by biological methods (32). There is bound (the largest proportion) and unbound (free) insulin in plasma (3) and also insulin antagonists, some of which are found in the plasma of the diabetic rat, cat or man. They disappear after hypophysectomy or adrenalectomy. Insulin antibodies neutralize insulin and produce hyperglycemia (34). Tissues also can inactivate insulin (insulinase action).

The secretion of insulin is governed by the level of the blood sugar and vice versa. The central nervous system is not necessary for the secretion of insulin, but the vagus nerve has a secondary and accesory role, causing a more rapid and perfect correction of changes in blood sugar (17).

Hypoglycemic conditioned reflexes have been obtained even in totally pancreatectomized dogs (1) but not after vagotomy (2).

PANCREATIC DIABETES - Total extirpation of the pancreas (29) provokes diabetes in all vertebrates, though its course and severity vary in different species (14). Diabetes is also observed when the β cells of the Langerhans islets are selectively destroyed (e.g. by alloxan) but not when the acinar cells are destroyed or the alpha cells are severely injured. Insulin antiserum can produce a temporary diabetes (34).

In pancreatic diabetes, the hormonal balance that regulates carbohydrate metabolism, is disturbed. Diabetes is due to the lack of insulin, and to the fact that activity of hormones (hypophyseal adrenal, etc.) that increase the severity of diabetes, is not balanced by the action of insulin. Proof of this is given by the fact that hypophysectomy or adrenalectomy decreases the severity of pancreatic diabetes.

After total pancreatectomy, when there is a complete lack of insulin while other hormones are active, the principal metabolic disturbances are: Hyperglycemia, glycosuria, deficient uptake and utilization of glucose by the cells, in spite of its abundance in

the plasma and tissue fluids. Production of sugar is not increased. Glycogen is diminished in the liver. Glycogen synthesis is slowed down in muscle, but it is deposited in larger than normal amounts in the heart, leukocytes and kidney. Fatty acids are not synthesized; transportation of fats from the depots to the liver is increased; there is hyperlipemia, fatty liver, intense hepatic ketogenesis and acidosis. Proteins are not synthesized, growth is arrested, protein catabolism is increased and there is wasting of tissues.

In the presence of sufficient quantities of insulin, protein and fat disturbances are slight or absent. The severity of diabetes is variable in different animal species.

A large part of the pancreas (up to 87 per cent in the dog and 95 per cent in the rat) can be removed without disturbing the normal blood sugar level; but in conditions of emergency the remaining pancreatic tissue cannot respond with an increase in insulin secretion as a normal pancreas does (19). Certain diabetogenic agents (hypophyseal hormones, thyroid, corticoids, excess of nutrients) provoke diabetes more readily in dogs with a pancreas which has been surgically reduced than in dogs with an intact pancreas. In most rats with 95 per cent of pancreas removed, a progressive diabetes occurs spontaneously in 1 to 3 months. Certain diabetogenic agents, given at adequate doses, produce hyperplasia of the islets and β cells. When this occurs diabetes caused by removal of 95 per cent of the pancreas in rats is prevented. These agents also can provoke regression of alloxanic diabetes (18). In larger doses they exhaust the islets and cause transitory or even permanent damage to their β cells. Hyperplasia of the islets is easily produced in rats, but only slight hyperplasia can be obtained in dogs.

Some agents diminish the incidence of diabetes in rats: restriction of calories, fractionation of meals, substances that increase free SH in tissues and various hormones. The incidence is increased by: excess of calories, factors that diminish SH, some fats, some

hormones.

When diabetes is produced by hormonal action on dogs, if the administration of the hormone is interrupted, the blood sugar falls from a diabetic to a normal level in 1 to 3 days, and the lesions of the β cells disappear progressively. This transitory and reversible diabetes is known as hypophyseal (or idiohypophyseal), thyroid, corticoid (or steroid), etc., diabetes, More prolonged treatment with hormones provokes permanent disturbances; interruption of treatment is not followed by disappearance of the diabetic condition, and the lessions in the β cells are irreversible and progressive. This is a pancreatic diabetes due to selective and permanent damage to the β cells. According to which is the causal agent, it is known as metahypophyseal (10) metathyroid (6), metacorticoid (20) or metasomatotropic (5) diabetes.

HYPOPHYSIS - The presence of hormones of the pars distalis (anterior lobe) of the pituitary gland prevents hypoglycemia and the decrease of glycogen during fasting; it also diminishes the action of hypoglycemic agents (insulin, phloridzin, fasting, etc.) (See Reviews in Houssay, 1942 and 1960).

In the absence of the anterior pituitary the body glucose pool is diminished; insulin (22) or fasting hypoglycemias are easily produced and are not corrected easily by adequate glucose output from the liver, as in normal animals. Convulsions, coma and death occurs if glucose is not given. Fasting hypoglycemias can be prevented by feeding a diet rich in carbohydrates or protein, but not by an exclusive fat diet. Hypophysectomized dogs are much more sensitive to the hypoglycemic and toxic actions of insulin than are adrenalectomized animals. Hyperglycemia provoked by adrenalin and other agents is less marked than in normal animals (see literature in Houssay, 1942).

In anterior pituitary insufficiency: a) protein anabolism and growth are strongly reduced, and in emergency conditions (diabetes, etc.) endogenous protein catabolism is only slightly increased; b) in pancreatic diabetes fat catabolism fatty, liver and specially

ketosis are strinkingly diminished.

Extirpation of the hypophysis or its anterior lobe (pars distalis) is followed by marked attenuation of pancreatic diabetes (30). There is: less fasting hyperglycemia and glycosuria,less need of insulin, no hyperlipemia nor fatty liver or kidney and remarkable reduction of ketosis, only slight increase of the excretion of nitrogen, longer survival, some utilization of sugar (30). In phloridzin glycosuria, ketonuria and urinary nitrogen excretion are diminished. In man the severity of diabetes is also alleviated by hypophysectomy or pituitary necrosis.

After pancreatectomy(in animal with hypophysis)hiperlipemia,fatty liver and kidney and severe ketosis are produced; insulin corrects these changes. Hypohysectomy prevents them in baboon(8)or rat. (30) and other species,but they reappear if corticoids or ACTH(in presence of adrenals) are injected to these rats but not by action of somatotropin (30).

Fatty liver reappear in pancreatectomized-hypophysectomized baboon partially with cortisone alone,completely with cortisone and thyroxine (8). The corticoids and not somatotropin are the active hormones in these animal species.

Fasting hypoglycemia, insulin sensitivity and atenuation of pancreatic diabetes following hypophysectomy are not due to predominance if insulin, because they take place in the absence of the pancreas (30), Hypophysectomized dogs have a smaller glucose pool and lower rates of glucose inflow from the liver to the blood and of glucose from the plasma to the cells than normal dogs (4). The peripheral consumption of glucose is slower in hypophysectomized dogs and is increased in rats and rabbits.

The hypersensitiveness to insulin has two causes: a)consumption of sugars is increased in tissues of hipophysectomized dogs; b) during hypoglycemia there is no rapid increase in glucose inflow from the liver to blood, as there is in normal dogs (4). All these disturbances are corrected by somatotropin (4).

The proper administration of extracts or hormones of pars distalis

corrects all the disturbances resulting from hypophyseal insufficiency; larger doses provoke disturbances in the opposite direction: resistance to insulin, adrenal hyperglycemia is increased; glycogen stores, specially those of muscle, are not depleted by fasting; this glycomyostatic action is observed also in the absence of the adrenals.

In certain conditions, hypophyseal extract or somatotropin produce in animals and man, a short lasting hypoglycemia and diminution of non esterified fatty acids (NEFA) (15);this "insulinoid" action is observed on the isolated rat diaphragm.After 2 to 4 hours, in man, blood sugar and NEFA increase; later resistance to insulin and diminished tolerance to glucose are observed. An inhibitory lipoprotein is produced which exists in the normal hypophysis and also in the blood of diabetic animals.

The diabetogenic activity of the hypophysis was discovered by Houssay and Biasotti, in 1930, who observed that: a) severity of pancreatic diabetes decreases following extirpation of the hypophysis or its pars distalis (in toads and dogs; and b)implantation or injection of pars distalis re-establishes the intensity of pancreatic diabetes attenuated by hypophysectomy or even increases it (in toads). These constituted the first demonstration that: a) pancreatic diabetes is due not only to lack of insulin, but also to the presence of hypophyseal hormones, which increases the severity of diabetes; b) pituitary hormones have a continuous physiological action on the carbohydrate metabolism in the normal and diabetic state; c)carbohydrate metabolism is regulated by a balance of hormones (pancreatic, hypophyseal, adrenal, etc.) which are in part antagonistic and in part synergic; d) in diabetes there is a disturbance in the balance of endocrine regulatory factors.

The diabetogenic activity of the pituitary gland and its hormones (somatotropin, corticotropin and prolactin) has been demonstrated in: a) hypophysectomized-pancreatectomized animals (and man)which are specially sensitive; b) easily in dogs, cats and other animals,

with previous ample pancreatectomy; c) in totally pancreatectomized dogs, which have severe diabetes and ketosis and die in 1 to 3 days; d) in normal dogs and cats (Young 1937), but not in normal rats or toads (10, 15).

The diabetogenic action of total pituitary extracts or of its diabetogenic hormones consists in: a) increase in insulin resistance; b) a decrease in glucose tolerance and consumption; c) hyperglycemia, glycosuria, ketonuria, polyuria; and d) hyperlipemia, fatty liver and kidney, (e) increased fat and protein catabolism. The full diabetes appears only after 2 to 4 days of daily injections, it does not occur if the animals are kept fasting. At first there is insulin resistance; lesions in the β cells of the islets of Langerhans appear later: degranulation, glycogen infiltration (hydropic vacuolization). When the lesions are intense, the content and secretion of insulin are strongly diminished (10).

Diabetogenic activity has been demonstrated with the following hormones; a) somatotropin (the most active in dogs and toads) and prolactin produce in cats or dogs transitory or permanent diabetes these effects are obtained in dogs without hypophysis and adrenals b) corticotropin is diabetogenic in pancreatectomized-hypophysectomized animals, but not in the absence of the adrenals. Corticotropin is more diabetogenic in rats, but somatotropin is active in dogs and cats and only exceptionally in rats. In rhesus and man, the somatotropins of bovine animals, cattle and swine are not active, but the monkey and human somatotropins produce hyperglycemia or diabetes in man and rhesus.

If treatment is discontinued diabetes disappears and the blood sugar returns to normal in 1 to 4 days. The β cells recover after a few more days and the pancreas contains and secretes normal amounts of insulin. This transitory diabetes was called: hypophyseal (Houssay) or idiohypophyseal (Young).

If hypophyseal treatment is kept up for a certain time, damage to the β cells becomes irreversible; the cells gradually disappear and

the islets contain few of them. When the treatment is interrupted, the diabetic state persists and becomes permanent. This diabetes is known as metahypophyseal diabetes. It was obtained first in partially pancreatectomized dogs (10) and later in dogs with an intact pancreas (35).

The hypophysis does not have a pancreatotrophic function. After hypophysectomy growth of the islets cease, but there is no atrophy of the islets nor diminution of insulin content and secretion. There is some atrophy of the acini, the islets tissue is proportionally larger owing to this atrophy, but the insular mass is not increased. Pituitary hormones produce in rats moderate hyperplasia of the islets and increase the insulin content of the pancreas.

Pituitary hormones have an extrapancreatic diabetogenic action as is proved by the following facts: a) they are active in pancreatectomized-hypophysectomized and in pancreatectomized dogs; b) resistance to insulin is observed before the islet lesions appear or the secretion of insulin decreases.

There is a certain antagonism between the pancreas and the pituitary in respect of diabetes: a) hypophysectomized dogs are very sensitive to insulin; b) reduction of the pancreatic mass markedly increases sensitiveness to the diabetogenic action of pituitary hormones. In other cases, as in growth, insulin and somatotropin are synergic.

Diabetes can not be produced, in toads, by pituitary hormones in the absence of the liver. Hypophyseal or metahypophyseal diabetic hyperglycemia falls to hypoglycemic level if the liver is removed.

Hypophyseal diabetogenic activity has been observed in hypophysectomized-pancreatectomized toads after removal of the digestive tract, lungs, kidney, thyroid, testicle, ovaries, encephalon and diencephalon. Hypophyseal diabetes has been provoked in thyroidectomized dogs; moreover, thyroidectomy does not improve dogs with metahypophyseal diabetes (15).

The adrenals exert a multiple influence on hypophyseal diabetes: a) adrenocorticotropin is diabetogenic in the presence of the adrenals;

b) corticoadrenal hormones are necessary for, or reinforce the diabetogenic activity of hypophyseal extract and of somatotropin; but we have obtained the diabetogenic action of somatotropin and of prolactin in partially pancreatectomized dogs without the hypophysis and adrenal (23); c) the presence of the adrenals or of cortical hormones facilitates considerably the diabetogenic action of the hypophysis in cats, dogs, and toads; d) summation of effects of hypophyseal and adrenal responses have been observed; c) in many cases, cortical hormones balance or regulate the action of the hypophysis (4).

Hypophyseal hyperfunction is the probable cause of diabetes in acromegaly. Coggeshall and Root (1940) mentioned glycosuria in 36 per cent and diabetes in 18.9 per cent of 53 cases of acromegaly. In the survey made by Atkinson (1938), glycosuria was found in 268 out of 817 cases published (32.8 per cent). Perhaps hypophyseal hyperfunction also exists in cases of diabetes beginning during a period of rapid growth. Hypophysectomy or destruction of pituitary by Itrium or a beam or protons, diminishes the intensity of diabetes and has been tried in cases of malignant diabetes. Corticotropin or human somatotropin injections increase the severity of human diabetes, specially after hypophysectomy. In some cases of diabetes in acromegalics there is insulin resistance, but not in others; probably, in the former hypophyseal hormones or plasma antagonists are active, just as in hypophyseal diabetics; on the other hand, insulin resistance would be normal in cases comparable to experimental metahypophyseal diabetes.

ADRENALS - Adrenal medulla can be extirpated without changes in the blood sugar level, glycogen content, blood sugar tolerance curve, intensity of diabetes: pancreatic, phloridzin or hypophyseal (15) Adrenalin secretion by the adrenal medulla, provoked in animals by several agents can provoke transitory hyperglycemias but not diabetes. In some human cases of pheochromocytoma diabetes has been observed and has been alleviated or has disappeared in a few observations,

after resection of the adrenal tumor.

The lack of cortical hormones by adrenalectomy produces changes similar to those of hypophysectomized animals: gradual decrease of glycemia and glycogen in fasting sensitivity to insulin (less than the hypophysoprived animals). Pancreatic diabetes is less severe (27) in adrenalectomized rat, dog, cat, toad and man. These animals have less marked hyperglycemia and glycosuria; inhibition of hiperlipemia fatty liver and ketonuria; diminution of the increase of protein catabolism, longer survival (27). Corticoid treatment increases the severity of this attenuated diabetes.

Repeated treatment with glucocorticoids can produce hyperglycemia, glycosuria insulin resistance and transitory diabetes in many animal species: rabbits, guinea pigs, chicks, rats; but slight hyperglicemia in cats and dogs. Corticotropin can also produce transitory diabetogenic effect in rats and man.

When the pancreas of dogs was surgically reduced to 16 to 23 per cent (average 20 per cent) of its initial weight, a transitory corticoid diabetes or a permanent metacorticoid diabetes can be produced, with reversible or irreversible β cells lesions (18).

The decreasing order of diabetogenic action is:dexametasone, triamcinolone, prednisolone, cortisol and cortisone.

Hyperplasia of the islets and β cells are produced by glucocorticoids or corticotropin in many species.In some animals there are no lesions of the β cells (rats), but in other species a reversible degranulation (guinea pig) or glycogen infiltration (corticoid diabetes in rabbits, metacorticoid diabetes in dogs).

With daily injections of appropriate doses of corticoids (compounds A.E,F, dexametasone or triamcinolone) during six months, hiperplasia of islets and β cells and prevention of diabetes was observed in a large proportion of subtotally pancreatectomized rats. There was an initial increase in incidence and severity of diabetes, but after some months, if the doses were not too high, the percentage of diabetes was considerably less than in the untreated controls (18)

During diabetogenic action of glucocorticoids the amount of glucose formed by gluconeogenesis from sources other than absorbed glucose, is approximately seven times the amount formed in normal rats (33). There is also impairment in the utilization of glucose and increase of resistance to insulin.

The action of corticoids may be diphasic. In subtotally pancreatectomized rat, large doses of glucocorticoids at first increase the incidence of diabetes but later, in a great number of cases, there is a smaller incidence and marked protection due principally to islets hyperplasia.

Corticoids almost always increase the severity of diabetes in the human subject, but in some cases a recuperation of tolerance or improvement of diabetes can be observed after some time of treatment.

It has not been proved that human diabetes is produced by adrenal hyperfunction; but its severity is increased by the existence of normal adrenal function. Adrenalectomy diminishes the severity of human diabetes and insulin repurement, and can arrest vascular lesions.

In high percentage of Cushing's disease and of hyperplasia or tumors of the adrenal,glycosuria or changes in the glucose tolerance curve have been reported. Subtotal or total extirpation of the adrenals usually improves glucose tolerance, and in some cases diabetes have disappeared or the insulin requirement is diminished or suppressed (31)

THYROID - The thyroid hormone increases the intestinal absorption of glucose and specially of galactose,level of blood sugar,tolerance curve and the rapidity of utilization of glycogen.

In human hyperthyroidism the fasting blood sugar level is often within normal limits, although values of 120-140 mg per 100 ml may occasionally be found without a coexistent diabetes. In blood tolerance curve the initial value can be high and, after sugar administration, the increase is supernormal, but the return to normal level is observed in two hours. This higher and slightly prolonged curve has been observed in 50-80 per cent of cases of hyperthyroidism

without diabetes (literature in Houssay, 1945, 1948). Slight spontaneous glycosuria has been found in 15 to 60 per cent of cases of hyperthyroidism (15). Joslin observed glycosuria in 38 per cent cases of primary hyperthyroidism and 28 per cent of secondary hyperthyroidism (24).

In dogs surgical thyroidectomy does not modify the severity of diabetes (11, 12); after iodothyroidectomy there is a slight and transitory diminution of hyperglycemia and requirement of insulin (15). In rats, surgical thyroidectomy or iodothyroidectomy diminishes markedly the incidence of alloxan diabetes and prevents in larger number of cases the appearance of diabetes after large (95 %) pancreatectomy (11,12,15). Iodothyroidectomy produces the regression of alloxan diabetes in rats (15). In man, thyroidectomy can improve the intensity of diabetes and the need of insulin.

Many antithyroideal substances (cysteine, thiouracil) exert an influence on diabetes partly by provoking hypothyroidism and by extrathyroideal action. These actions are connected with an increase of free SH in tissues (13).

The degradation of insulin is diminished by thyroidectomy and some sulphur compounds. The degradation is accelerated by thyroxine and triiodothyronine (7).

In animals with intact and healthy pancreas thyroid administration does not produce diabetes (11, 12). Transient glycosuria has appeared in man undergoing thyroid treatment.

Daily administration of thyroid can produce diabetes in dogs only when the resistance of the pancreas has been previously diminished: a) by resection of 80-87 per cent of the mass of pancreas; b) by previous recent alloxan or pituitary or thyroid diabetes (11,12). This thyroid diabetes is transitory and disappears a few days after the administration of thyroid has ceased; but if the thyroid treatment is continued long enough the lesions of β cells become irreversible and when the treatment is suspended, the dogs remain with a permanent diabetes, metathyroid diabetes, and the pancreas does not secrete more insulin (11, 12).

In thyroid and metathyroid diabetes the liver is the source of hyperglycemia. Hepatectomy produces a fall of the blood sugar until low levels and hypoglycemic symptoms occur.

Administration of thyroid gland or thyroxine increases the severity of all types of experimental or human diabetes, glycosuria, polyuria and ketonuria increase markedly.

Thyroid treatment produces hypertrophy and hyperplasia of the β cells in many species (rats), but little or none in others (dogs). In rats, after large pancreatectomy (95%), it is possible with adequate dose to observe an initial aggravation of the diabetes and in a second stage, an improvement or cure of it.

Diabetes is not a cause of hyperthyroidism (11). The incidence of hyperthyroidism was 1.2 per cent in 42.800 cases of diabetes (24) But in hyperthyroidism ther is an increase of frequency of diabetes, which was present in 2.5 per cent of cases of primary hyperthyroidism (24) and in 4.3 to 5.6 per cent of adenomatous goiter with hyperthyroidism (24).

When hyperthyroidism and diabetes are simultaneously present in a subject, they exert a mutually unfavorable influence and each condition must be carefully treated. Control of hyperthyroidism (surgery, antithyroid drugs, I^{131}) decreases markedly the intensity of diabetes, life is prolonged, hyperglycemia, glycosuria and ketonuria diminish, and insulin requirement is smaller.

SEX HORMONES -. Sex hormones have a definite action on the evolution of diabetes consecutive to subtotal pancreatectomy (95 %) in the white rat. The ovary and estrogens diminish the frequency of this diabetes; the testicle and androgen increase its frequency and severity. A combined treatment with estrogen and insulin produces regression of a large proportion (65 %) of alloxan diabetes (18). The protective action of estrogen is due to the hyperplasia of islets (β cells) and increase of insulin; they have also some action on pituitary and other glands or organs (15, 18).

The capacity of hyperplasia and regeneration of islets is much more accentuated in rats than in cats and is less accentuated in dogs. In

rats diabetes prevention (in subtotally pancreatectomized)or regression (in alloxanic diabetes) can be obtained by estrogens or corticoids, due to the hyperplasia of β cells.

GENERAL STATEMENT - In all forms of diabetes there is an insufficiency of insulin in relation to the needs of the organism. The deficiency is absolute when there is lack of insulin secretion. The deficiency is relative: a) when insulin secretion is diminished; b) when insulin is inactivated by binding or by antibodies c) when the secretion is normal, but the requeriment of insulin is increased; and d) when there is resistance of cells to insulin action.

In diabetes there is also an imperfect regulation of the endocrine secretion of the pancreas, since it cannot adjust itself to the needs of the organism in order to bring about a normal blood sugar level.

In all forms of diabetes, pituitary and adrenal secretion,whether normal or not augment diabetes. All the endocrine glands play part in all diabetic conditions, either directly because of their specific function or through their influence on other organs.

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SUMMARY

ROLE OF ENDOCRINE GLANDS IN EXPERIMENTAL DIABETES

Bernardo A. Houssay

Diabetes is a disturbance of the endocrine balance which regulates carbohydrate, fat and protein metabolism.

Diabetic hyperglycemia cannot be produced or maintained in absence of the liver.

In all forms of diabetes there is an insufficiency of insulin in relation to the needs of the organism, and the internal secretion of pancreas is unable to adjust itself in order to bring about a normal sugar level.

In absence of pituitary gland or adrenals the normal carbohydrate content of the body and the blood sugar level are not maintained in fasting. Pancreatic diabetes is attenuated, specially there is no fatty liver and only a slight increase of ketogenesis.

Excess of somatotropin, corticotropin or prolactin can produce diabetes in dog, cat, etc. and human somatotropin in man, specially if the pancreatic mass is reduced. The diabetes is first transitory and later permanent (metahypophyseal diabetes, with irreversible β cells lesions).

Cortical hormones can produce transitory increase of hyperglycemia (corticoid diabetes). If pancreatic mass is reduced, permanet diabetes (metacorticoid diabetes) is obtained.

Thyroid hormone can produce only slight transitory hyperglycemia or glycosuria. Diabetes (transitory or permanent) is obtained in dogs, only if the mass of islets is reduced (partial pancreatectomy) or recently damaged.

In subtotally pancreatectomized rats, ovary or estrogens diminish

the frequency of diabetes; testicle or androgens increase its frequency and intensity.

In animals (rats) whose pancreas can hypertrophy easily the islets (and β cells), diabetes prevention (in subtotally pancreatectomized) or regression (in alloxanic diabetes) can be obtained by estrogens or corticoids, specially if associated with insulin.

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